IN THE UNITED STATES PATENT OFFICE

In re Application J. K. MEHRA *et al.*.
Metoprolol Manufacturing Process

Serial No. 10/807,221
Filed 23 March 2004

DECLARATION

I, Janakraj Karamchand MEHRA, hereby swear as follows:

1. I am an inventor of record of the captioned patent application.

2. In 1963, I was awarded a Doctor of Philosophy degree (Technical) from Mumbai University, (Mumbai, India) under the guidance of Professor S. V. Sunthankar. I subsequently worked at the National Chemical Laboratory (Pune, India) and completed post-doctoral research in organic chemistry at Columbia University (New York City, U.SA.) under the guidance of Professor. Charles Dawson. Since then, I have worked for over thirty years as a pharmaceutical research chemist and as a manager of pharmaceutical research and of pharmaceutical manufacturing. I therefore believe that I am one of skill in the art of pharmaceutical chemistry.

3. I have reviewed the 30 December 2005 OFFICE ACTION and the art of record in this case.

Novelty requirement under 35 U.S.C. Sec.102 (b)

4. The method of US5082969 teaches the first step reaction at a temperature of 0-25°C (please see examples and claims). Further, the method of US 6252113 clearly states the reaction is to be carryout at a temperature range of 50-70 °C (for reasons of purity, please see description at col.2, lines 45-54 and claims). On the contrary, the instant invention clearly claims carrying

out the reaction at 42.5+2.5 °C. Thus we believe that the cited methods cannot be said to anticipate the instantly claimed temperature range.

5. Further, one of skill in the art would read RIBALTO BARO *et al.*, Examples 1-2 to teach a process forming 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane contaminated with about 15-20% chlorohydrin compound. In contrast, the process of the instant invention yields essentially a single product, 3-[4-(2-methoxyethyl)phenoxy]-1.2-epoxypropane. Because the impurity yields are so different the method of US5082969 patent cannot be said to anticipate the instantly claimed method.

6. Furthermore, none of the cited methods discloses washings of the product at the specific pH range as claimed in the instant application for removing the impurities in the product (before employing the first step reaction product in the next stage). The cited references neither suggest nor imply such washing of product till a specific pH range will improve the quality of product. Thus the cited methods cannot be said to anticipate the instantly claimed pH range.

Obviousness rejection under 35 U.S.C. Sec. 103(a)

7. The advantages of the instant invention over the method of RIBALTO BARO *et al* are shorter reaction times; significant reduction of the reactants quantities used; limited or no contamination of chlorohydrins in the epoxy-intermediate 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane; and the purity of the resulting epoxide compound. For example, the percentage of contaminating chlorohydrins in the method of Ribalto Baro *et al* is 15 to 20% (pl. see examples and claims), in contrast to that it is formed only 0.5 to 1 % in the instant invention method. One of skill in the art would not have expected these advantages based on the teachings of the prior art.

8. The method of PALMÉR *et al.*, on the other hand, teaches to carry out the reaction at a temperature range of 50-70 °C and having advantage of shorter reaction time. However, PALMÉR teaches distillation of the epoxide intermediate, namely 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane, for sufficient purity in order to pursue for metoprolol base formation. PALMÉR does not teach water washings as an alternative to distillation of the intermediate compound under high vacuum. Also, PALMÉR fails to suggest or imply a process using the claimed pH range for water washings would improve the purity of the intermediate epoxide compound. To the contrary, PALMÉR emphasizes distillation of the intermediate compound as the only possible solution to achieve purity. *See* PALMÉR *et al* at col.2 lines 51-54. PALMÉR neither suggests nor implies the claimed solution.

9. The advantages of the instant invention over PALMÉR are: elimination of industrially unfriendly high vacuum distillation of product that requires special arrangements; and significantly improved yield & purity of intermediate as well as final metoprolol, which was made possible only with the claimed improvements. One of skill in the art would not have expected these advantages based on the teachings of PALMÉR alone nor combined with RIBALTO BARO.

10. It appears that the examiner considers distillation of epichlorohydrin in the instant invention and distillation of intermediate epoxide compound to be equivalent processes. This is not, however, correct. PALMÉR discloses the distillation of the end-product, not distillation of an intermediate reactant (epichlorohydrin). This alone is a sufficient showing that PALMÉR does not anticipate the claimed invention.

11. The art of record fails to teach that an adjustment of the pH of the water washings to the specific claimed range. The claimed improvement results into improved purity and avoids an industrially unfavorable process step of distilling the intermediate epoxide under high vacuum and that too with a 2-8% fore-cut. *Cf.* PALMÉR *et al.* at claims and specification. The art of record fails to show that one of skill in the art would have had a reasonable expectation of success with this process modification.

12. Similarly, RIBALTO BARO teaches to use isopropyl amine in about 16 molar excess to the starting epoxide. In contrast, but the claimed invention makes possible lowering the amounts of isopropyl amine significantly. This totally eliminates the need to use a pressure vessel, an apparatus required by the prior art methods. *See* RIBALTO BARO *et al*, col 2, lines 24-28 and example #2).

Unexpected Synergistic Results

13. PALMÉR and Ribalta Baro *et al.* are respectfully believed to support the patentability of our method. A side-by-side comparison of our invention and the process of PALMÉR, at col. 2, lines 45-54 shows that our invention produces a significantly greater yield and purity without the need for distillation of epoxy-intermediate 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane. Our process enables an yield of up to 93 to 95%, with a purity from 97 to 99% in case of 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane. *See* instant specification at example 1. In contrast, PALMÉR at column 2, lines 45-54 and examples, concedes only 80% yield with a purity of 96 to 98% in the first step.

14. A side by side comparison of our invention with process of RIBALTO BARO *et al.* examples 1 and 2 indicates that our process is more economical and environmentally friendly. The RIBALTO BARO method itself is inferior in achieving higher purity as taught/observed by

others (*see* admissions of PALMÉR *et al.*) such as: the intermediate contamination of with chlorohydrins; longer reaction times; use of volatile isopropyl amine in large excess (16 times *vs* 5.5 times by molar weight in the claimed invention) to effect metoprolol base forming reaction; and the purity of intermediate compound.

15. Our results would not have been expected by one of skill in the art.

16. There is a nexus between this evidence and the pending patent claims, because this evidence would be considered by one of skill in the art to have probative value in showing the pending patent claims are non-obvious in light of the art of record.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

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Janakraj Karamchand MEHRA, Ph.D.
Dated as of 20 March 2006

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others (*see* admissions of PALMER *et al.*) such as the intermediate contamination of with chlorohydrins; longer reaction times; use of volatile isopropyl amine in large excess (16 times vs 5.5 times by molar weight in the claimed invention to effect metoprolol base forming reaction; and the purity of intermediate compound.

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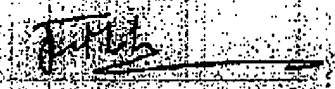

Jayakrisna Karamchand MEHRA, Ph.D.
Dated as of: 20 March 2006